EL474185815US 10/069328 Rec'd PCT/PTO 22 FEB 2002

FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: 55025/31671

U.S APPLICATION NO. (If known, see 37 CFR 1.5): 10/069328

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/00865	March 9, 2000	August 24, 1999

TITLE OF INVENTION
COMPOSITIONS CONTAINING ESTERS FOR TREATING PARASITIC INFESTATIONS OF ORGANISMS

APPLICANT(S) FOR DO/EO/US
GARNETT, David John

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 – 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information: Return Postcard; Power of Attorney (unsigned)

JC19 Rec'd PCT/PTO 22 FEB 2002

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/069328	PCT/GB00/00865	55025/31671

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) – (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

CALCULATIONS PTO USE ONLY		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$	890.00
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	32 - 20 =	12	x $18.00	$	216.00
Independent claims	3 - 3 =	0	x $80.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$	1,236.00
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$	
SUBTOTAL =				$	1,236.00
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	1,236.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	$	
TOTAL FEES ENCLOSED =				$	1,236.00
			Amount to be refunded:	$	
			charged:	$	

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 20-0823 in the amount of $1,236.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 20-0823. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to review (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Kenneth Solomon
Thompson Coburn LLP
One Firstar Plaza
St. Louis, Missouri 63101-1693

SIGNATURE

Kenneth Solomon
NAME

31,427
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this correspondence and the documents referred to as enclosed therein are being deposited with the United States Postal Service on February 22, 2002 2001 in an envelope as 'Express Mail Post Office To Addressee' Mailing Label Number EL474185815US addressed to: BOX PCT, Assistant Commissioner for Patents, Washington, D.C. 20231.

Kenneth Solomon
Type or Print Name

Signature

Application of:	Garnett	**Group No.:**	Unknown
Serial No.:	Unknown	**Atty. Docket No.:**	55025/31671
Filed:	February 22, 2002		
For:	COMPOSITIONS CONTAINING ESTERS FOR TREATING PARASITIC INFESTATIONS OF ORGANISMS	**Examiner:**	Unknown

BOX PCT
Commissioner of Patents and Trademarks
Washington, DC 20231

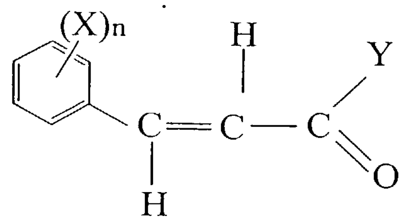
PRELIMINARY AMENDMENT

This paper is submitted as a Preliminary Amendment in the above-identified application which is a national stage filing under 35 USC §371 of PCT/GB00/00865. It is respectfully requested that the following amendment to the claims be entered as indicated below and that the application be examined on the merits.

In the Claims

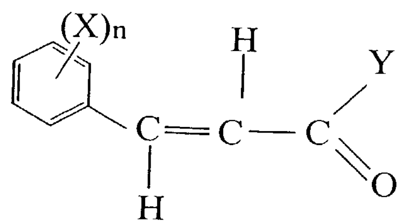
Claims 1-18 are cancelled and claims 19 – 50 have been added as indicted on the attached sheet.

19. (New) Use of a compound of the general formula:



wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, for the treatment of parasitic infestations of livestock.

20. (New) Use of the compound of the general formula:



wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, for the treatment of parasitic infestations selected from the group consisting of *Psoroptes sp., Sarcoptes sp., Dermanyssus gallinae and Varroa jacobsoni oudemans (Varroa destructor).*

21. (New) Use of the compound as defined in claim 1 for the treatment of parasitic infestations selected from the group consisting of *Psorptes sp., Sarcoptes sp., Dermanyssus gallinae* and *Varroa jacobsoni oudemans (Varroa destructor).*

22. (New) Use of the compound as defined in claim 1 for the combined treatment of *Psoroptes sp.* and Sarcoptes sp. infestations in livestock.

23. (New) Use of the compound as defined in claim 1 for the treatment of infestations caused by the eggs of blowflies.

24. (New) Use of the compound as defined in claim 5 for the combined treatment of scab mite infestations and fly strike.

25. (New) Use of the compound as defined in claim 1, wherein the compound is *trans*-cinnamic acid ethyl ester.

26. (New) Use of the compound as defined in claim 1, wherein the compound is provided as a dilutable emulsion.

27. (New) Use of the compound as defined in claim 8, wherein the emulsifier is sodium lauryl sulphate, Triton-X-100 or lecithin.

28. (New) Use of the compound as defined in claim 8, wherein the emulsifier is included in an amount 1 to 5 wt. %.

29. (New) Use of the compound as defined in claim 10, wherein 3 wt. % of the formulation is emulsifier.

30. (New) Use of the compound as defined in claim 8, wherein the emulsion is applied as a spray.

31. (New) Use of the compound as defined in claim 8, wherein the emulsion is applied as a dip.

32. (New) Use of the compound as defined in claim 8, wherein the emulsion is applied as a dip, diluted dip emulsion contains the active compound at a concentration of 0.1 to 10%.

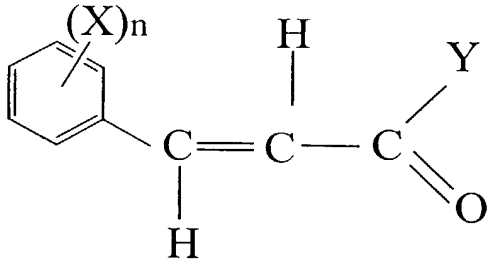
33. (New) Use of the compound as defined in claim 1, wherein the compound is included with an oily ointment or aqueous cream for topical application.

34. (New) Use of the compound as defined in claim 1, wherein the compound is introduced into the infested organism by means of a wick based evaporator whereby the compound is vaporized in a sufficient concentration to kill the parasite but does not produce toxic effects in the infested organism.

35. (New) The use of the compound as defined in claim 1 in combination with other active agents.

36. (New) The use of the compound as defined in claim 17, wherein the other agent is allyl propionate.

37. (New) A method of treating livestock suffering from parasitic infestation comprising applying to the livestock a compound of the general formula:



wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, thereby destroying the parasite.

38. (New) A method as claimed in claim 19 wherein the parasite is selected from the group consisting of *Psorptes sp., Sarcoptes sp., Dermanyssus gallinae* and *Varroa jacobsoni oudemans (Varroa destructor)*.

39. (New) A method as claimed in claim 19 for the combined treatment of *Psorptes sp.,* and *Sarcoptes sp.*, infestations in livestock.

40. (New) A method as claimed in claim 19 for the treatment of infestations caused by the eggs of blowflies.

41. (New) A method as claimed in claim 22 for the combined treatment of scab mite infestations and fly strike.

42. (New) A method as claimed in claim 19 wherein the compound is trans-cinnamic acid ethyl ester.

43. (New) A method as claimed in claim 19 wherein the compound is provided as a dilutable emulsion.

44. (New) A method as claimed in claim 25 wherein the emulsifier is selected from the group consisting of sodium lauryl sulphate, Tritox-X-100 and lecithin.

45. (New) A method as claimed in claim 25 wherein the emulsion is applied as a spray.

46. (New) A method as claimed in claim 25 wherein the emulsion is applied as a dip.

47. (New) A method as claimed in claim 19 wherein the compound is included with an oily ointment or aqueous cream for topical application.

48. (New) A method as claimed in claim 19 wherein the compound is introduced into the infested organism by means of a wick based evaporator whereby the compound is vaporized in a sufficient concentration to kill the parasite but not produce toxic effects in the infested organism.

49. (New) A method as claimed in claim 19 wherein other active agents are applied to the livestock in combination with the compound.

50. (New) A method as claimed in claim 31 wherein the other agent is alkyl proprionate.

Remarks

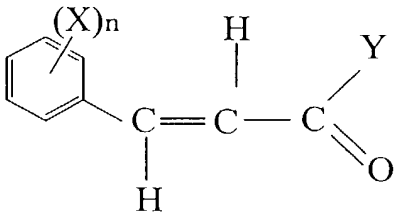
Claims 1 – 18 have been cancelled. New claims 19 – 50 has been added. It is respectfully requested that the amendment above be entered and the application be examined on the merits. Should any questions arise or if Applicants or Applicants' attorney can facilitate in the examination of this case, please contact the undersigned attorney.

Respectfully submitted,

Kenneth Solomon, Reg. #31427
Thompson Coburn LLP
One Firstar Plaza
St. Louis, Missouri 63101
Telephone: 314-552-6297
Fax: 314-552-7297

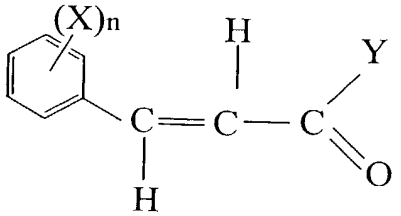
NEW CLAIMS

19. (New) Use of a compound of the general formula:



wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, for the treatment of parasitic infestations of livestock.

20. (New) Use of the compound of the general formula:



wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, for the treatment of parasitic infestations selected from the group consisting of *Psoroptes sp., Sarcoptes sp., Dermanyssus gallinae and Varroa jacobsoni oudemans (Varroa destructor).*

21. (New) Use of the compound as defined in claim 1 for the treatment of parasitic infestations selected from the group consisting of *Psorptes sp., Sarcoptes sp., Dermanyssus gallinae* and *Varroa jacobsoni oudemans (Varroa destructor).*

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23. (New) Use of the compound as defined in claim 1 for the treatment of infestations caused by the eggs of blowflies.

24. (New) Use of the compound as defined in claim 5 for the combined treatment of scab mite infestations and fly strike.

25. (New) Use of the compound as defined in claim 1, wherein the compound is *trans*-cinnamic acid ethyl ester.

26. (New) Use of the compound as defined in claim 1, wherein the compound is provided as a dilutable emulsion.

27. (New) Use of the compound as defined in claim 8, wherein the emulsifier is sodium lauryl sulphate, Triton-X-100 or lecithin.

28. (New) Use of the compound as defined in claim 8, wherein the emulsifier is included in an amount 1 to 5 wt. %.

29. (New) Use of the compound as defined in claim 10, wherein 3 wt. % of the formulation is emulsifier.

30. (New) Use of the compound as defined in claim 8, wherein the emulsion is applied as a spray.

31. (New) Use of the compound as defined in claim 8, wherein the emulsion is applied as a dip.

32. (New) Use of the compound as defined in claim 8, wherein the emulsion is applied as a dip, diluted dip emulsion contains the active compound at a concentration of 0.1 to 10%.

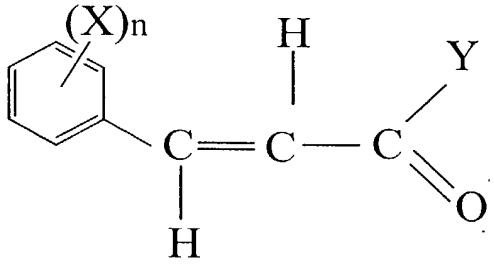
33. (New) Use of the compound as defined in claim 1, wherein the compound is included with an oily ointment or aqueous cream for topical application.

34. (New) Use of the compound as defined in claim 1, wherein the compound is introduced into the infested organism by means of a wick based evaporator whereby the compound is vaporized in a sufficient concentration to kill the parasite but does not produce toxic effects in the infested organism.

35. (New) The use of the compound as defined in claim 1 in combination with other active agents.

36. (New) The use of the compound as defined in claim 17, wherein the other agent is allyl propionate.

37. (New) A method of treating livestock suffering from parasitic infestation comprising applying to the livestock a compound of the general formula:



wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, thereby destroying the parasite.

38. (New) A method as claimed in claim 19 wherein the parasite is selected from the group consisting of *Psorptes sp., Sarcoptes sp., Dermanyssus gallinae* and *Varroa jacobsoni oudemans (Varroa destructor)*.

39. (New) A method as claimed in claim 19 for the combined treatment of *Psorptes sp.*, and *Sarcoptes sp.*, infestations in livestock.

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41. (New) A method as claimed in claim 22 for the combined treatment of scab mite infestations and fly strike.

42. (New) A method as claimed in claim 19 wherein the compound is trans-cinnamic acid ethyl ester.

43. (New) A method as claimed in claim 19 wherein the compound is provided as a dilutable emulsion.

44. (New) A method as claimed in claim 25 wherein the emulsifier is selected from the group consisting of sodium lauryl sulphate, Tritox-X-100 and lecithin.

45. (New) A method as claimed in claim 25 wherein the emulsion is applied as a spray.

46. (New) A method as claimed in claim 25 wherein the emulsion is applied as a dip.

47. (New) A method as claimed in claim 19 wherein the compound is included with an oily ointment or aqueous cream for topical application.

48. (New) A method as claimed in claim 19 wherein the compound is introduced into the infested organism by means of a wick based evaporator whereby the compound is vaporized in a sufficient concentration to kill the parasite but not produce toxic effects in the infested organism.

49. (New) A method as claimed in claim 19 wherein other active agents are applied to the livestock in combination with the compound.

50. (New) A method as claimed in claim 31 wherein the other agent is alkyl proprionate.

COMPOSITIONS CONTAINING ESTHERS FOR TREATING PARASITIC INFESTATIONS OF ORGANISMS

DESCRIPTION

The present invention relates to compounds for the improved treatment of infestations, particularly but not exclusively infestations of crops, livestock and domestic animals such as stored grain, sheep and poultry.

A number of types of insects and mites are parasitic and may infect both domestic and farm animals causing serious health problems to the animal if left untreated. Some species burrow into the skin of the animal whilst other pierce the skin causing irritation and inflammation. These lesions are suscepticle to additional fungal or secondary insect infection. Thus there is a need for a treatment for insect and mite infestations that also provides anti-mycotic or mycostatic action. Insect and/or mite infestation and fungal contamination of crops, stored grains and food also has a serious adverse economic effect.

Psoroptes ovis is an ectoparasite of sheep causing psoroptic mange that causes inflammation and surface exudation, severe pruritus, wool loss, restlessness, biting and scratching of infested areas leading ultimately to death of the sheep in as little as 4-6 weeks. Another type of mite, namely *Varroa* infects beehives and afflicts *Apis mellifera* in many countries of the world.

Conventionally, organophosphates and synergised pyreithrins have been used to treat infestations. However, organophosphates have been implicated in the etiology of medical conditions in humans and must be handled with great care. Although synergised pyreithrins are generally considered to be a much safer alternative to the use of

organophosphates, such compounds have been associated with deleterious effects on the environment, especially if allowed to enter the water system.

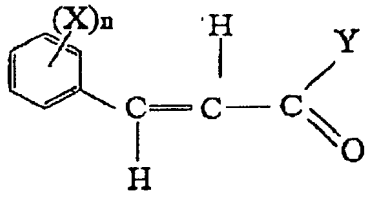
Animals, particularly sheep, may also suffer from blowfly strike (*ovine mysiasis)*. Primary ovine strike is a cutaneous infestation by the larvae of green bottles (*Ovis aries)* of domestic sheep. The fly larvae infest and actively feed on the tissues and secretions of the animal. In temperate regions, such as Great Britain, the most common species responsible for this cutaneous infestation is the primary strike species *Lucilia sericata* Meigen (Diptera: Calliphoridae). Animals struck by the blowfly and left untreated may suffer from chronic ammonia toxicity leading ultimately to death. In England and Wales, 80% of farms are affected by this ectoparasite per annum, with 1.6% of all sheep being struck every year. Thus, this cutaneous infestation is a a significant threat to livestock.

It is an aim of the present invention to provide compounds for an improved treatment against parasitic infestations which are safer to use and less damaging to the environment.

A further aim of the present invention is to provide compounds that not only provide a treatment against parasitic infection but also provide simultaneous treatment against secondary fungal infection.

Accordingly, the present invention provides compounds for the treatment of parasitic infestations, the compounds having the general formula:-

ART 34 AMDT



wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, in the preparation of a medicament for the treatment of parasitic infestations selected from the group consisting of *Psoroptes sp., Varroa jacobsoni oudeman, Dermanyssus gallinae and Sarcoptes sp.*

The preferred compound is *trans*-cinnamic acid ethyl ester.

Additionally, the compounds have been found to be effective as a fungicide. This enables the compounds to be used to treat a combination of parasitic infestations in a diverse range of organisms such as poultry, sheep and bees and simultaneously reduce and/or prevent secondary fungal infection.

The compounds may be administered in a variety of forms depending upon the intended application of the compound. For example, the compound may be provided as a dilutable emulsion, being mixed with water and/or a suitable emulsifier such as sodium lauryl sulphate or lecithin. Such an emulsion may be used as a spray to treat organisms infested with, for example, mites or blowfly eggs, such as *Lucilia sericata,* or

alternatively as a dip, particularly for the treatment of sheep. Preferably, a dip emulsion contains the active compound at a concentration of 0.1 to 10%.

Preferably, the concentrated formulation is at least 40 wt.% of the active compound and at least 40 wt.% water. More preferably, 50 wt.% of the formulation is made up of the active compound. Preferably, 1-5 wt.% of triton X-100 or powdered (de-oiled) lecithin is included in the formulation, more preferably 3 wt.%. If lecithin is used, it is preferable to use a chemically or enzymatically hydrolyzed type. Other compounds, such isopropyl alcohol or polyethylene glycol esters, may also be used in the formulation. The concentrated emulsion may then be diluted as appropriate for the intended application.

The formulation preferably includes minor amounts of an anti-oxidant, such as ascorbic acid or, more preferably, butylated hydroxytoluene (BHT) and/or preservatives, such as Nipagin, proprionic acid or Parabens.

Alternatively, solid formulations may be provided, for example for the treatment of stored grain or the like. The compound may be mixed with an inert carrier, such as silica talc.

The compound may alternatively be introduced into the area containing the infested organism by means of a wick based evaporator whereby the compound is vapourised in a sufficient concentration to kill the parasite but does not produce toxic effects in the infested organism. The compound may also be absorbed or adsorbed on material for slow release into the region of infestation. The compound may alternatively be included with an oily ointment or an aqueous cream for topical treatment of animals.

The active compounds may also be used in combination with other agents, such as allyl proprionate, to augment its activity.

The present invention will now be further illustrated by means of the following Examples in which Example 1 relates to the use of the preferred compound of the present invention for the control of the mite *Psoroptes cuniculi* , Example 2 relates to the use of the preferred compound of the present invention for the control of the mite *Acarus siro,* Example 3 relates to the use of the preferred compound of the present invention in the control of the mite *Varroa jacobsoni oudemans* Example 4 relates to the use of the preferred compound of the present invention in the control of *Lucilia sericata* infestation in sheep, and Example 5 relates to the antifungal activity of the preferred compound of the present invention, and with reference to the accompanying drawings in which:-

Figure 1 is a diagram illustrating the mean LT_{50} for the mite *Psoroptes cuniculi* following their immersion in a range of concentrations of the compound *trans*- cinnamic acid ethyl ester;

Figure 2 is a diagram illustrating the proportion of *P. cuniculi* which were dead (± s.e.) 24 hours after immersion in a range of concentrations of *trans*-cinnamic acid ethyl ester;

Figure 3 is a diagram illustrating the mean LT_{50} (± s.e) for the mite *P. cuniculi* for adult males (1), adult females (2) and female nymphs (3);

Figure 4 is a diagram illustrating efficacy of the compound *trans*-cinnamic acid ethyl ester against the eggs of the primary agent of sheep myiasis *Lucilia Sericata* after exposure for 1 minute expressed using the probit transformation;

Figure 5 is a diagram illustrating efficacy of the compound *trans*-cinnamic acid ethyl ester against the eggs of the primary agent of sheep myiasis *Lucilia Sericata* after exposure for 1 minute without using probit transformation;

Figure 6 is a diagram illustrating efficacy of the compound *trans*-cinnamic acid ethyl ester against the eggs of the primary agent of sheep myiasis *Lucilia Sericata* after exposure for 30 minutes; and

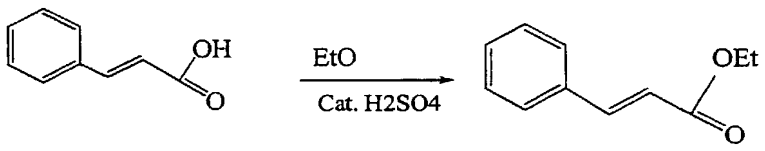
Figure 7 is a diagram illustrating efficacy of the compound *trans*-cinnamic acid ethyl ester against the eggs of the primary agent of sheep myiasis *Lucilia Sericata* after exposure for 90 minutes.

The present invention provides an effective treatment for a wide range of parasites, such as mites and the larvae of blow flies which cause detrimental effects to, inter alia, animals and insects. Additionally, the invention provides a treatment that also has antifungal activity.

The compound *trans*-cinnamic acid ethyl ester or ethyl cinnamate has been found to control infestation of mites in diverse organisms such as sheep, rabbits and bees. The compound is also effective against *L.sericata* eggs which cause a cutaneous infestation in sheep. Advantageously, the compound may be used on wounds and open lesions of animals without injury. This is unexpected since organic esters normally impede the healing of a lesion and/or produce toxic effects in the sheep. The compound may be provided in a variety of compositions depending upon the organism to be treated.

Experimental. – Preparation of *trans*-Cinnamic Acid Ethyl Ester.

Trans-cinnamic acid ethyl ester is prepared in the conventional manner from the esterification of cinnamic acid with ethanol and a catalytic quantity of sulphuric acid, as illustrated in Scheme 1 shown below:-



Scheme 1

Example 1.

A series of *in vitro* assays were conducted to examine the effects of the compound *trans*-cinnamic acid ethyl ester on the mite *Psoroptes cuniculi*. This mite infests rabbits and is very similar to the mite *Psoroptes ovis* which infests sheep and causes sheep scab.

The mites were taken from the ears of infested rabbits and exposed for 24 hours to the active compound at concentrations of 10, 1 or 0.1 % (V/V). The concentrations were obtained by serial dilution of the compound in 0.05% sodium dodecyl sulphate (SDS). It was found that 100, 74 and 20% of the mites had died respectively compared to 8% following exposure to the control (0.05% SDS only), as illustrated in Figure 1 of the accompanying drawings.

Exposure of the mites to concentrations of 10% and 1% of the ethyl ester resulted in 50% mortality (LT_{50}) after 0.5 days and 1 day respectively, compared to an LT_{50} of approximately 2.5 days following exposure to 0.1% of the compound (V/V) or the control (0.05% SDS only). This is illustrated in Figure 2 of the accompanying drawings. Immersion of the mites in the compound for 1, 30 or 90 minutes showed no significant difference in either the LT_{50} or the proportion dead 24 hours after the exposure thus

demonstrating that exposure of the mite to the compound for one minute is as effective as exposure for 90 minutes.

The LC_{50} (concentration required to produce 50% mortality) 24 hours after exposure to the ethyl ester was 2.21% (95% confidence interval 1.73-2.92%), as shown in Table 1 below. The LC_{95} was 6.29% (95% confidence interval 4.98-8.88).

Table 1

LD	**Concentration (% V/V)**	**95% Confidence Interval**
25	0.53	-0.15 – 1.01
50	2.21	1.73 – 2.92
75	3.88	3.12 – 5.31
95	6.29	4.98 – 8.88

Figure 3 of the accompanying drawings shows the mean LT_{50} (± s.e) for the mites at different stages of the life cycle. Line (1) represents adult males, line (2) adult females and (3) female nymphs. The mortality of the various life cycle stages of the mites was not significantly different in the first 24 hour exposure to the compound. However, the results indicated that beyond the first 24 hour period female nymphs had a lower mortality rate than adult males or females.

Thus, *trans*-cinnamic acid ethyl ester gives greater than 50% levels of mortality within 24 hours, for all life cycle stages of P. *cuniculi* after short contact times (1 min) at concentrations of 2.2% (V/V). At one minute contact time, concentrations of greater than 6% (V/V) are required to bring about mortality of greater than 95%. Recent theoretical analysis using simulation modelling (Wall, unpublished) has shown that sustained

mortality of greater than 50% per day is required to suppress a growing population of *P. ovis*. Hence, the use of the compound in its present formulation as an effective control agent for *P. ovis* may require either use in relatively high concentrations (>6% V/V) or, if used at lower concentrations, on the presence continued residual activity on the host animal.

Example 2.

The effect of *trans*-cinnamic acid ethyl ester on the mite *Acarus siro* was investigated using a residual filter paper bioassay. Seven samples of 0.01g of mite culture was placed on 7, 90mm Whatman™ filter papers. Each paper was previously treated with 745µl of a solution containing *trans*-cinnamic acid ethyl ester at concentrations varying from 74.64µl to 7.64 x 10^{-4} µl/petri dish respectively and allowed to dry for 15 minutes. The controls were treated in the same way except ethanol (HPLC grade) was used as this was sample dilutant. Percentage control was calculated as in W.S. Abbot, A Method of Computing the Effectiveness of an Insecticide, Journal of Economic Entomology (1925) 18, 265-267.

Table 2a below shows the efficacy of the compound against the mite *in vitro*. At a concentration of 7.64µl/petri dish, *trans*-cinnamic acid ethyl ester was found to be effective resulting in a percentage control figure of 100%.

Table 2a

Concentration (µl)	Mean Percentage Mortality Over Control
3.20×10^{1}	100.00
3.20	95.57
3.20×10^{-1}	97.74
3.20×10^{-2}	69.51
3.20×10^{-3}	32.95
3.20×10^{-4}	6.33

A further study was carried out to investigate the effect of Ethyl cinnamate on the grain/flour mite *Acarus siro* using a residual filter paper bioassay. Mites from a colony grown at 25°C ± 85% RH were removed using a spatular and placed into a petri dish. 275 µ of the cinnamate was placed onto a filter paper in one well of a 6 well (17 ml) cell culture plate and likewise, 275 µ of DH_20 was placed on another piece of 4 cm Whatman filter paper in a second well. Mixed instars (male + female) were added to each well. The actual number of instars was unknown in each case, since the test only sought to establish the presence of activity; measured in terms of cidal effect (knockdown). The duration of the test was 5 ± days. Both treatments were incubated at 25°C ± 85% RH and each well was checked 4 times daily. Small amounts of food mix of yeastea 20B and wheat germ in the ratio 3 : 1 were included on the filter paper in both treatments.

The treatment was later modified : 2, 10 cm Whatman filter papers were cut to ø of 3 cm and placed in the mite culture. After 10 minutes they were removed using

forceps. The mites were then swept into each well respective of treatment. The cinnamate provided too glutenous (viscous) to be used undiluted. Therefore, it was dissolved using 10 fold dilutions in ethanol. Therefore 30 μ cinnamate : 270 μ ethanol to the extent of 10^{-4}. The control was ethanol.

The above experiment was repeated. The results are given in Table 2b below.

Table 2b

Concentration	**% mortality**
Ethanol control	24.00
10^{-1}	100.00
10^{-2}	100.00
10^{-3}	98.40
10^{-4}	86.00

The results above are very conclusive. Ethyl cinnamate is toxic to mites even at dilutions of 10^{-4}. It is now clear that *Acarus siro* can receive 100% mortality from an undiluted dose of Ethyl cinnamate in less than 15 minutes approximately.

Additionally, it was also noted that Ethyl cinnamate is toxic to insects, at least mealworms, T.molibr. However, the concentrations tested were 10^{-1}; 10^{-2}. 5 mealworms were placed onto each filter paper treatment. Although all were of the same instar, the 10^{-1} individuals were slightly larger. They did not die and after two days moulted. 10^{-7} did die. Therefore, the size of larvae appears to be important.

Example 3.

The *trans*-cinnamic acid ethyl ester may also be used to control Varroa mite infections in bee hives caused by the *Varroa jacobsoni oudemans* mite which afflicts *Apis mellifera* in many countries of the world. The compound may be introduced into the hive using a simple wick based evaporator such as the Nassenheider Evaporator which produces a concentration of vapour in the hive which will kill the mites but not produce toxic effects on the bees. The compound is found naturally in Storax Oil and other plant material and therefore may be considered to be a safer treatment for control of the mites than the use of organophosphates or synergised pyreithrins.

The safety of the compound in man has also been determined using LD_{50} assays using four animal species. Table 3 below illustrates the results of the assays. Additionally, the ethyl ester compound produced no sensitization after a 24 hour closed-patch test on 25 human volunteers (Kligman 1973). The compound has also been used in the food industry without safety problems for many years and is listed in the Food Chemical Index.

Table 3

ROUTE	SPECIES	LDSO	REFERENCE
Oral	Rat	7800mg/kg	Russell 1973
Oral	Mouse	4000mg/kg	VPITAR 33(5)48,74
Oral	Guinea Pig	4000mg/kg	VPITAR 33(5)48,74
Dermal	Rabbit	>5000mg.kg	FRMM

Example 4.

A series of *in vitro* tests were carried out to investigate the effects of the compound *trans*-cinnamic acid ethyl ester on the hatching of eggs of *L.sericata*.

A blowfly culture originating from the Central Veterinary Laboratory based in Weybridge, Surrey was used for the tests. None of the original adults had previously been exposed or resistant to insecticides. Eggs aged 10±2 hours of the blowfly were harvested on pig's liver in clusters using a prolene 4/0 paintbrush and examined under the binocular microscope for suitablility. Adult females used to produce these eggs were kept at 20°C, rh 70±5%, with a photoperiod of 8 hours. Groups of 30 eggs were then immediately transferred to a 9-cm Whatman filter paper in a 9-cm plastic petri dish. Two ml of cinnamic acid ethyl ester at concentrations in the range 1.0%; 2.5%; 5.0%; 7.5% and 10.0% V/V was poured gently into the petri dish immersing the eggs. Each concentration was previously prepared by dilution of active compound in a 2.0% W/V aqueous lecithin solution pre-warmed to 20°C. The mixture was sonicated for two minutes. After an exposure time of 1 minute, the test solution was carefully poured off and the eggs recovered individually to a 7ml polythene container in which a filter paper was saturated with pig's liver washings. The L_1 larvae were prevented from escaping by the presence of a 2-cm square piece of cotton cloth, secured in place by the lid of the container which had a 4mm square hole cut out to allow air to enter. Eggs following treatment were incubated at 25°C, rh 70±2% with a photoperiod of 8 hours duration. Hatching typically occurred within 12 hours of treatment.

Each concentration was replicated twice; controls were treated using only lecithin solution. The whole experiment was repeated using two further exposure times of 30

minutes and 90 minutes respectively. Fresh lecithin solution was prepared every day to ensure that bacterial activity did not influence the result.

The data were analysed using fitted curve graphical analysis. LC50 values were calculated from these data. The data gathered from the experiment with an exposure time of 1 minute was also expressed using the probit transformation. However, the remaining data collected from the experiments did not support such analysis due to high egg mortality.

All data was treated according to Abbot W.S. (1925 J. Econ. Ent. 18, 265-267) and expressed as corrected mortality but did not support probit analysis with the exception of exposure time of one minute.

Fitted curves were used to calculate the concentration required to kill 50% of the eggs, (LC50) using the data obtained after immersing the eggs in solutions ranging from 1.0% to 10.0% V/V. The median lethal concentrations, (LC50) and LC95 concentrations are shown in Table 4 below:-

Table 4

Lethal Concentrations at 1 minute	**Lethal Concentrations at 30 minutes**	**Lethal Concentrations at 90 minutes**
LC50 2.76%	LC50 1.78%	LC50 0.36%
LC95>7.50%	LC95>5.00%	LC95 2.91%

Figures 4, 5 and 6 of the accompanying drawings show efficacy of the compound on the eggs of *L.sericata* after exposure for one minute, thirty minutes and ninety minutes respectively. The graphs show all replicate treatments and demonstrate the trend of

increasing mortality as both concentration and exposure time increase. Exposure of the eggs to a concentration of 2.91% V/V provides 95% mortaility at 90 minutes.

The proportion of dead eggs after immersion was analysed using a multiple analysis of variance; (ANOVA) using both concentration and immersion time as factors after arc transforming the corrected mortality data. Both concentration and exposure time are significant, ($p=<0.001$ in both cases respectively).

Hence, the compound is effective against the eggs of blowflies. However, the agent was found to be ineffective against all stages of blow fly and larval life cycle. It was therefore unexpected that the compound would have an effect on the eggs of the flies. The compound has not previously be used specifically as an ovicide. Its use as an ovicide for the treatment of animals has a major advantage over previous treatments in that it minimizes damage to the skin and tissues of the animals since this is mainly caused by the larvae of the blowfly.

Example 5

The antifungal activity of ethyl trans-cinnamate against a number of different fungi was investigated by means of in a simple growth inhibition test.

The following quantities of Ethyl trans-Cinnamate were added to Sabourand Dextrose agar (SAB); 50 ml L^{-1}, 4ml L^{-1}, 2ml L^{-1}, lml L^{-1}, 400 µl L^{-1}, 200 µl L^{-1} and 40 µl L^{-1}. The addition of Ethyl trans-Cinnamate did not effect the pH of the Media. These were then autoclaved and poured into standard Petri dishes. Loss of Ethyl trans-Cinnamate due to evaporation during autoclaving was found to be negligible. Duplicate plates of each concentration, plus control plates containing only SAB Agar, where then separately inoculated with, four different species of fungi, these were *Aspergillus*

nidulans, *Penicillium digitatum, Rhizopus arrhizus* and *Fusarium culmorum*. Inoculation was carried out using a single stab at the centre of each Petri dish. The plates were then incubated at 30°C for 6 days and daily measurements of mycobial growth where taken every 24 hours. In the case of *Penicillium digitatum*, the presence or absence of growth was recorded, as this species does demonstrate clear radial growth.

The levels of growth for each species, at tested concentrations of Ethyl trans-Cinnamate, are shown in Tables 5a-5d below.

Table 5a

Day	Level of Radial Growth (mm) of *A. nidulans*							
	50 ml L^{-1}	4ml L^{-1}	2ml L^{-1}	1ml L^{-1}	400µl L^{-1}	200µl L^{-1}	40µl L^{-1}	Control
1	0	0	0	0	0	0	0	2.0
2	0	0	0	0	5.5	9.5	12.0	12.5
3	0	0	0	6.0	11.5	16.5	23.0	22.5
4	0	0	0	11.5	18.0	23.0	27.0	27.0
5	0	0	6.5	16.5	24.5	28.0	32.5	32.5
6	0	4.5	12.5	22.0	30.0	34.5	38	40.0

Table 5b

Day	Level of Radial Growth (mm) of *F. culmorum*							
	50 ml L^{-1}	4ml L^{-1}	2ml L^{-1}	1ml L^{-1}	400µl L^{-1}	200µl L^{-1}	40µl L^{-1}	Control
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	1	1
4	0	0	0	0	1	1	1	1
5	0	0	0	0	2	2	2	2
6	0	0	0	0	6	6	6	6

Table 5c

Day	Level of Radial Growth (mm) of *R. arrhizus*							
	50 ml L^{-1}	4ml L^{-1}	2ml L^{-1}	1ml L^{-1}	400µl L^{-1}	200µl L^{-1}	40µl L^{-1}	Control
1	0	0	1.	8.5	14.5	18.0	26.0	30.0
2	0	23.5	45.0	45.0	45.0	45.0	45.0	45.0
3	0	45.0	45.0	45.0	45.0	45.0	45.0	45.0
4	0	45.0	45.0	45.0	45.0	45.0	45.0	45.0
5	0	45.0	45.0	45.0	45.0	45.0	45.0	45.0
6	0	45.0	45.0	45.0	45.0	45.0	45.0	45.0

45.5mm Growth = Total Plate Coverage.

Table 5d

Day	Growth of *P.* digitatum							
	50 ml L^{-1}	4ml L^{-1}	2ml L^{-1}	1ml L^{-1}	400µl L^{-1}	200µl L^{-1}	40µl L^{-1}	Control
1	-	-	-	-	-	-	-	+
2	-	-	-	-	+	++	++	++
3	-	-	-	-	++	++	++	++
4	-	-	-	+	++	++	++	++
5	-	-	-	+	++	++	++	++
6	-	-	-	+	++	++	++	++

- = No Growth, + = Growth, ++ = Extensive Growth

It is clear from the results shown in Tables 5a-5d above that Ethyl trans-Cinnamate has an antifungal effect on all four of the different species of fungi tested. At the 50ml L^{-1} level there is complete inhibition of growth in all four fungi. Further experiments (data not shown) showed that this effect continued for at least 8 days at this, and higher, doses. Additionally, there is a clearly dose response in the growth of all four fungi. This is particularly clear in *A. nidulans* and the 24h growth of R. *arrhizus*, which show increasing levels of growth.

The data suggests that Ethyl trans-Cinnmnate may be a mycostatic agent, at least at low doses, rather than mycocidal, as all the fungi continue to grow (below 50 ml L^{-1}) during the experiment, albeit at a slower rate. This is also suggested by the fact that the

fast growing *R. arrhizus* covers the plates after only 2 days at the 2ml L^{-1} dose, whilst the slower growing *A. nidulans*, and the very slow growing *F. culmorum*, never reach this level of growth, the Ethyl trans-Cinnamate having less effect on the faster growing species. Therefore it can be concluded that Ethyl trans-Cinnamate is a very effective antifungal at a dose of 50ml L^{-1} and above. This efficacy is reduced as dose is reduced, as would be expected, but a limited effect is still seen at doses as low as as 40µl L^{-1}.

Thus, the compounds of the present invention provide an effective means of controlling parasitic infestations in a number of very different organisms. In particular, the compounds can be used for the combined treatment of infestation, such as scab mite infestation and fly strike, as well as any secondary fungal infection. Moreover, the compounds are an improvement over those compounds previously used for treating infestations because the compounds are non-toxic and environmentally friendly. The compound is particularly useful for inclusion in a sheep dip to prevent/reduce infestation of sheet by Psorptes or Sarcoptes (mange), especially since the treatment does not impede healing of any lesions present on the sheep nor produce any toxic effects. Additionally, the compound is not harmful to the environment. This is important since many chemicals that have previously been included in sheep dips to treat infestation, such as organophosphate, and pyreithrins are environmentally toxic.

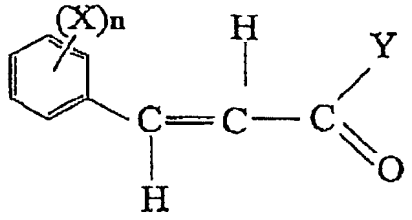
The active compound can be provided in various formulations depending upon its intended purpose and is suitable for use in food, feedstuffs and for animal use due to its low toxicity and low impact on the environment. A concentrated emulsion, e.g. for use as sheep dip, may contain 50% (w/w) *trans-cinnamic* ethyl ester with 47% water and 3% Triton X-100 or powdered (de-oiled) lecithin. Such formulations will typically contain

small amounts of an anti-oxidant (such as ascorbic acid or butylated hydroxytoluenc) and a preservative (such as Nipagin, propionic acid or Parabens). The emulsion may be prepared by mixing the various quantities in a high speed blender, such as an Ultra-Turrex homogeniser. Once the high concentration emulsion are obtained, the liquid is then suitable for dilution as appropriate for the application. Solid formulations may also be produced, e.g. for the treatment of stored grains. The active compound is mixed with an insert carrier, such as silica talc, wherein the compound is adsorbed to the particles evenly thereby enabling a well mixed active to be achieved as a dust or powder. Furthermore, the active compound may be included within an oily ointment or in an aqueous cream for topical treatment of domestic animals and/or livestock.

ART 34 AMDT

CLAIMS

1. Use of the compound of the general formula:-



wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, in the preparation of a medicament for the treatment of parasitic infestations selected from the group consisting of *Psoroptes sp., Sarcoptes sp., Dermanyssus gallinae* and *Varroa jacobsoni oudemans*.

2. Use of the compound as defined in claim 1 for the combined treatment of *Psoroptes sp.* and *Sarcoptes sp.* infestations in livestock.

3. Use of the compound as defined in claim 1 or claim 2 for the treatment of infestations caused by the eggs of blowflies.

4. Use of the compound as defined in claim 3 for the combined treatment of scab mite infestations and fly strike.

5. Use of the compound as defined in any one of claims 1 to 4, wherein the compound is *trans*-cinnamic acid ethyl ester.

6. Use of the compound as defined in any one of the preceding claims wherein the compound is provided as a dilutable emulsion.

7. Use of the compound as defined in claim 6, wherein a concentrated formulation of the emulsion is at least 40 wt.% of the compound and at least 40 wt.% water.

8. Use of the compound as defined in claim 7, wherein the formulation is at least 50 wt.% of the compound.

9. Use of the compound as defined in claim 6, 7 or 8, wherein the emulsifier is sodium lauryl sulphate, Triton-X-100 or lecithin.

10. Use of the compound as defined in claim 9, wherein the emulsifier is included in an amount 1 to 5 wt.%.

11. Use of the compound as defined in claim 10, wherein 3 wt.% of the formulation is emulsifier.

12. Use of the compound as defined in any one of claims 6 to 11, wherein the emulsion is applied as a spray.

13. Use of the compound as defined in any one of claims 6 to 11, wherein the emulsion is applied as a dip.

14. Use of the compound as defined in claim 13, wherein the diluted dip emulsion contains the active compound at a concentration of 0.1 to 10%.

15. Use of the compound as defined in any one of claims 1 to 5, wherein the compound is included with an oily ointment or aqueous cream for topical application.

16. Use of the compound as defined in any one of claims 1 to 5, wherein the compound is introduced into the infested organism by means of a wick based

evaporator whereby the compound is vaporized in a sufficient concentration to kill the parasite but does not produce toxic effects in the infested organism.

17. The use of the compound as defined in any one of the preceding claims in combination with other active agents.

18. The use of the compound as defined in claim 17, wherein the other agent is allyl propionate.

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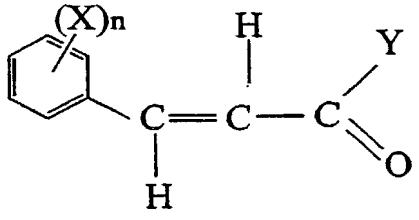
(54) Title: COMPOSITIONS CONTAINING ESTERS FOR TREATING PARASITIC INFESTATIONS OF ORGANISMS



(I)

(57) Abstract: Use of the compound of general formula (I) wherein Y is an alkoxy group having 1 to 4 carbon atoms, a hydroxyl group, an amine group, a halide group or a nitro group; X is a hydroxyl group, an amine group, a halide group, a nitro group, an alkoxy group or an ester group and n is 0 or 1, in the preparation of a medicament for the treatment of parasitic infestations of organisms.

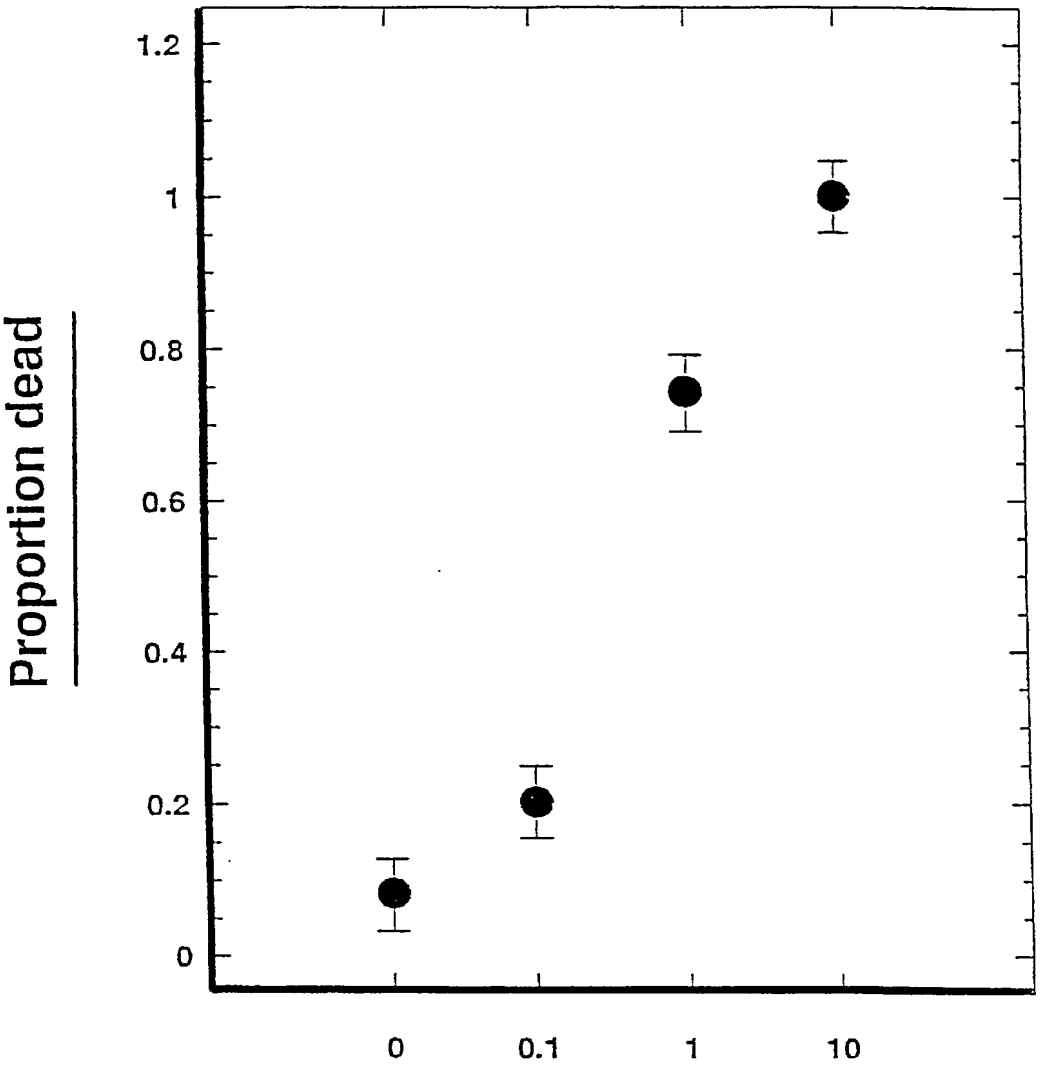


FIG. 1

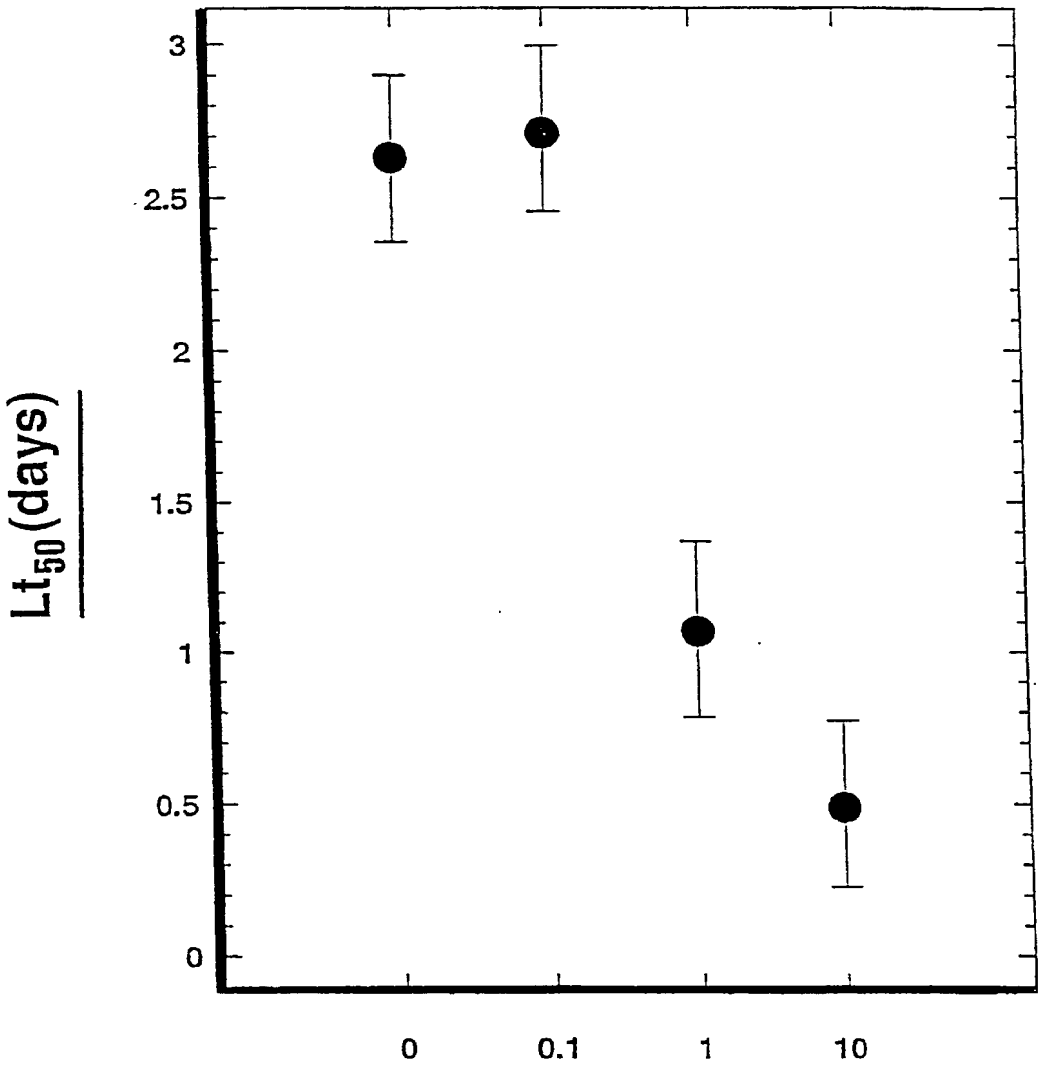


FIG. 2

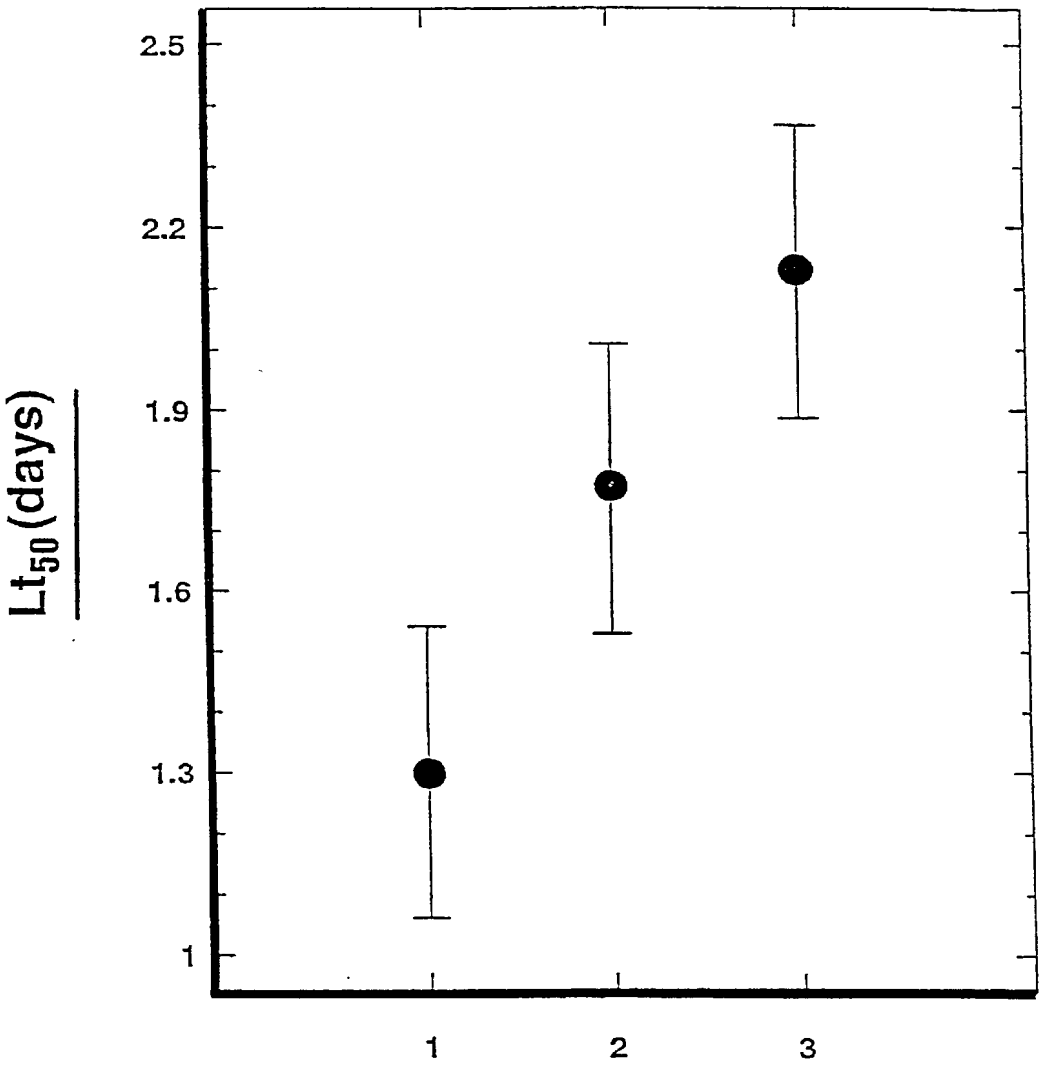


FIG. 3

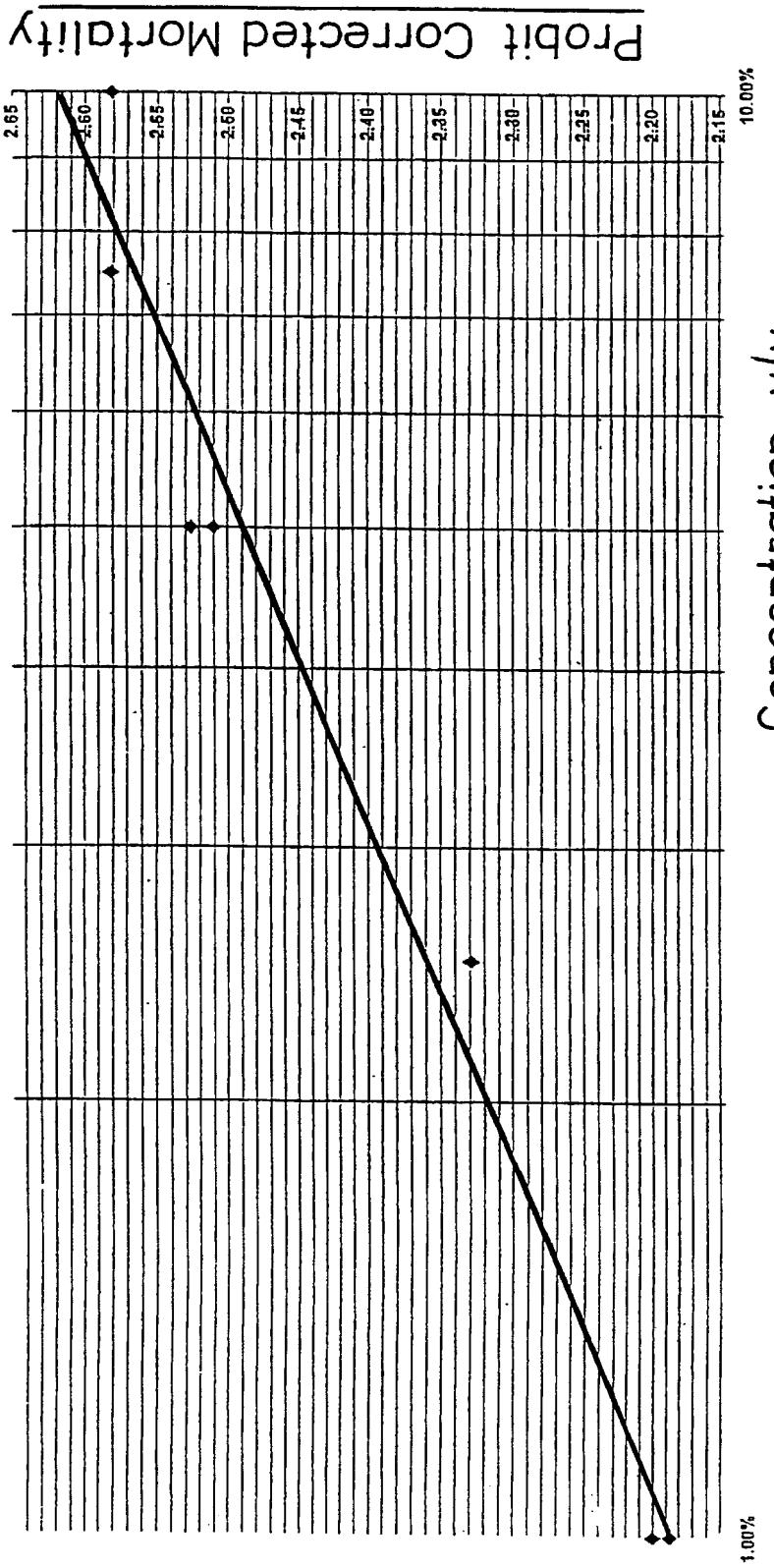

Probit Corrected Mortality
2.65
2.60
2.55
2.50
2.45
2.40
2.35
2.30
2.25
2.20
2.15
10.00%
1.00%
Concentration v/v

FIG. 4

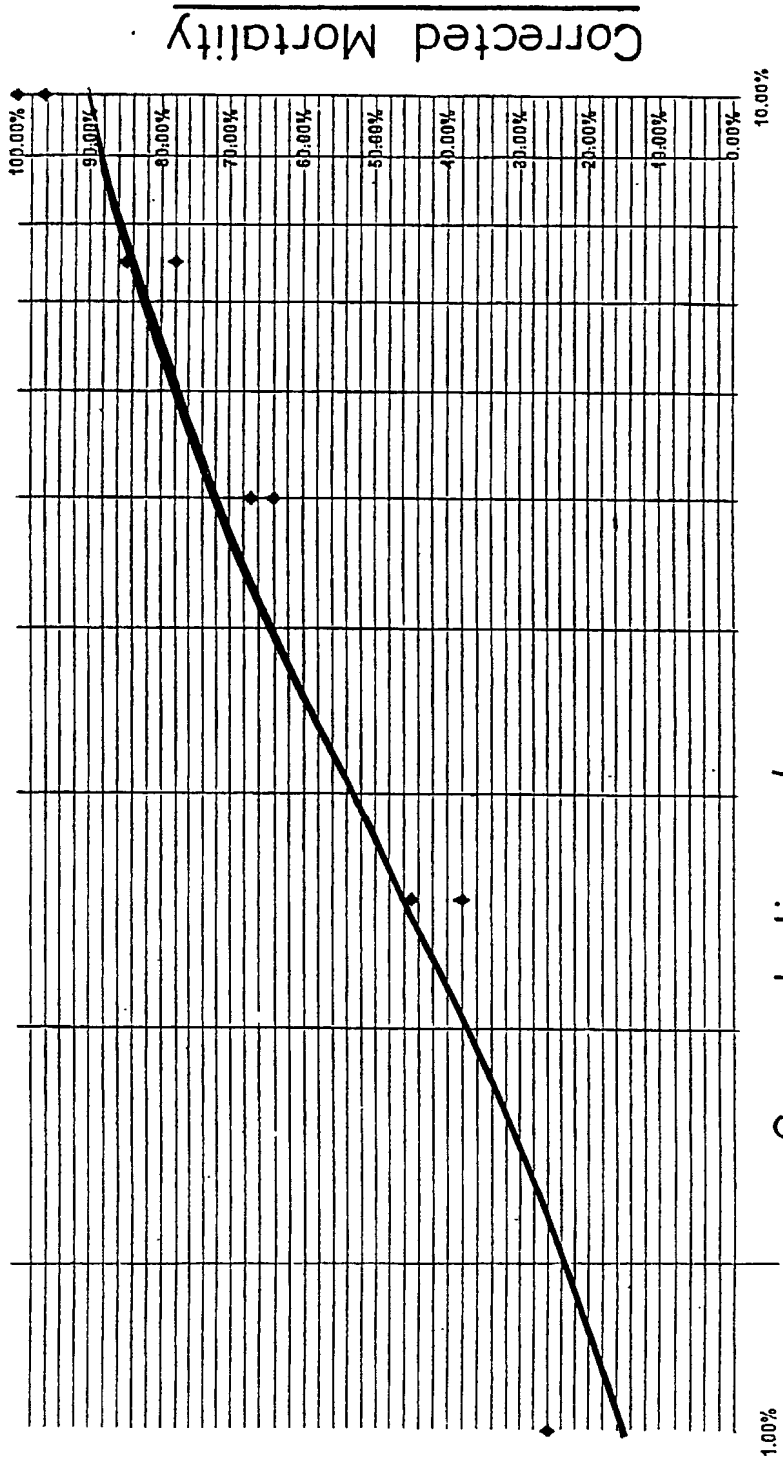

Corrected Mortality
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
10.00%
1.00%
Concentration v/v

FIG.5

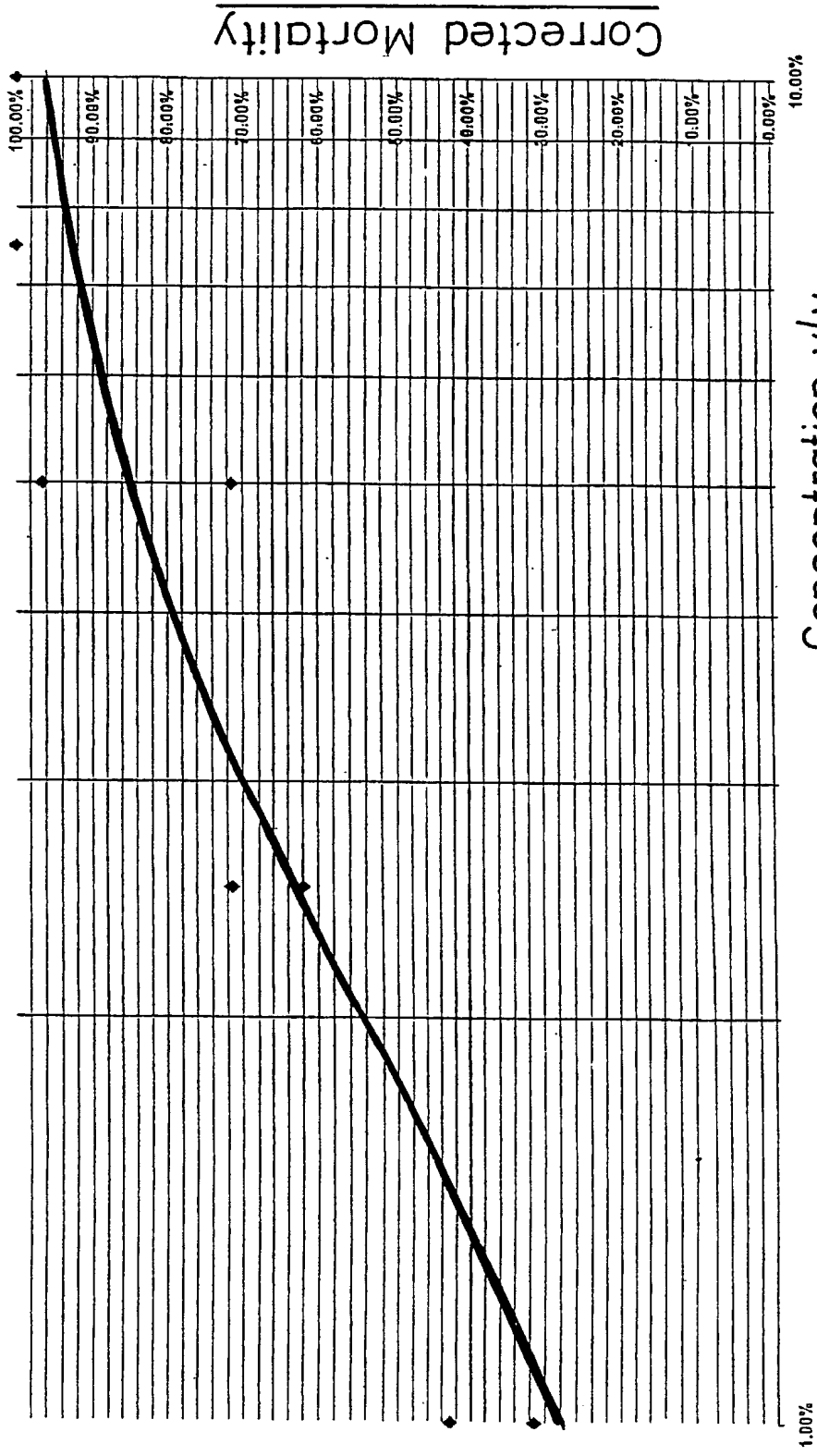

Corrected Mortality
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
10.00%
1.00%
Concentration v/v

FIG.6

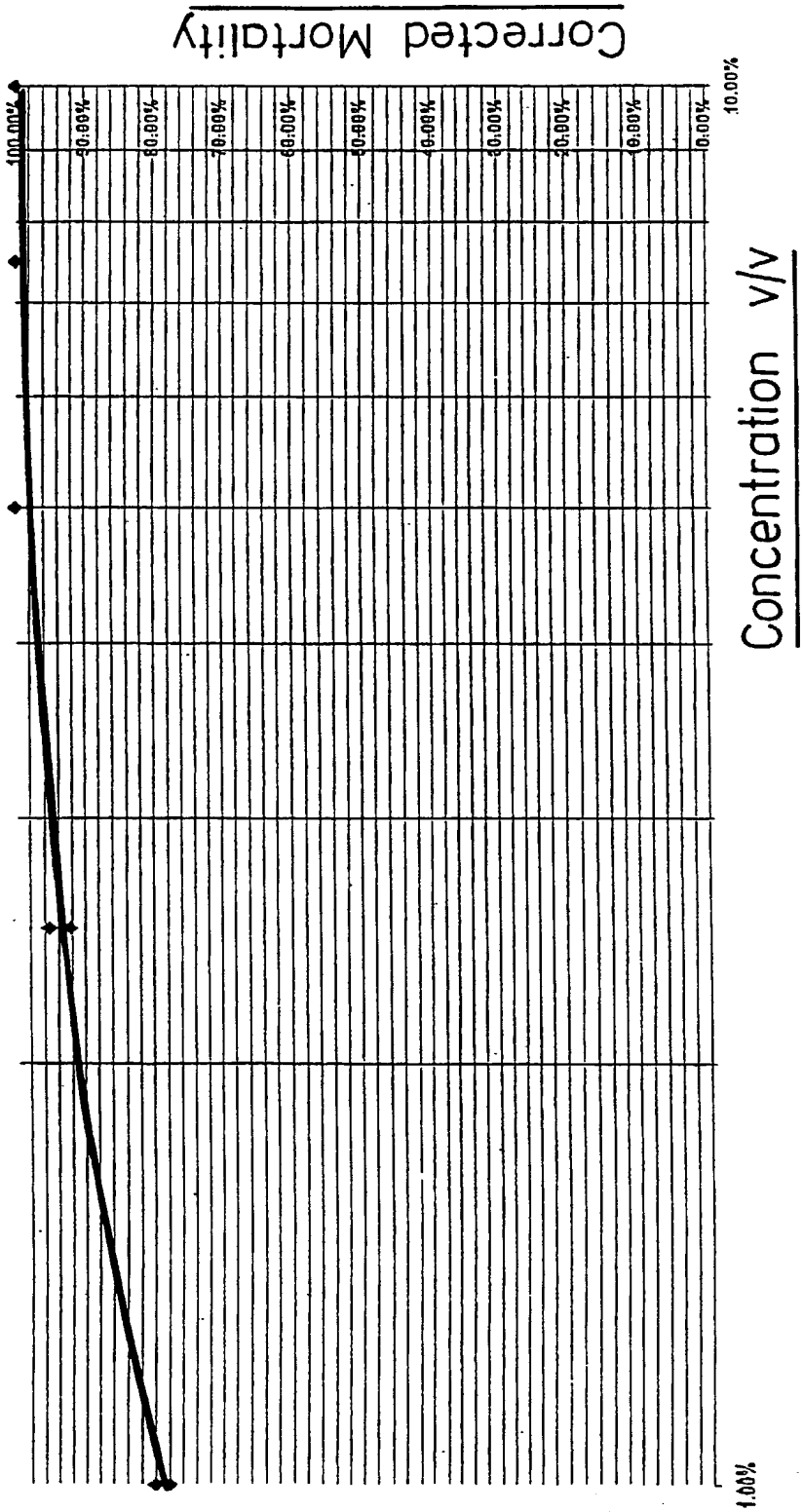

Corrected Mortality
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
10.00%
1.00%
Concentration v/v

FIG. 7

Rec'd PCT/PTO 12 JUN 2002

PTO/SB/01 (03-01)
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DECLARATION FOR UTILITY, DESIGN, DIVISIONAL AND CONTINUATION-IN-PART PATENT APPLICATIONS (37 CFR 1.63)	**Attorney Docket Number**	55025/31671
	First Named Inventor	Garnett
☒ Declaration Submitted with Initial Filing	***COMPLETE IF KNOWN***	
	Application Number	10/069,328
☐ Supplemental Declaration Submitted ☐ Declaration Submitted for Continuation-In-Part Filing ☐ Declaration Submitted for Divisional Filing	Filing Date	February 22, 2002
	Group Art Unit	To Be Assigned
	Examiner Name	To Be Assigned

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

David J. Garnett
Rose Cottage, Goginian,
Aberystwyth, Ceredigion SY23 3NY
Great Britain

COMPOSITIONS CONTAINING ESTERS FOR TREATING PARASITIC INFESTATIONS OF ORGANISMS

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) February 22, 2002 as United States Application Number or PCT International Application Number 10/069,328 and was amended on (MM/DD/YYYY) February 22, 2002 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
01/13913 A1	WO	3/9/2000	☐	☐	☒
9906080.8	GB	3/17/1999	☐	☐	☒
9919889.7	GB	8/24/1999	☐	☐	☒

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

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DECLARATION — Utility or Design Patent Application

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR : ☐ A petition has been filed for this unsigned inventor

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Inventor's Signature D. Garnett **Date** 19/5/02

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NAME OF SECOND INVENTOR : ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) **Family Name or Surname**

Inventor's Signature **Date**

Residence: City **State** **Country** **Citizenship**

Mailing Address

City **State** **ZIP** **Country**

☐ Additional inventors are being named on the ____ supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.

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